REMARKS

This paper is being filed in response to the Office Action dated June 23, 2008, the period for response to which is set to expire on September 23, 2008. Claims 1-37 are pending, claims 27-31 are withdrawn. Claims 14 and 25 are amended and claims 15 and 26 are canceled. Claims 1-28 and 35-37 have been rejected. New claims 38 and 39 have been added. Upon entry of this amendment, claims 1-14, 16-25, 27, 28 and 35-39 will be pending and in condition for allowance.

Applicant appreciates the Examiner's rejoinder of various claims, but would continue to rebut and/or traverse the remaining aspects of the restriction requirement, including the Examiner's corresponding statements, for reasons provided previously and below, and for others as well. Enclosed herewith is a Supplemental Information Disclosure Statement, together with corresponding fee.

Rejection under 35 USC § 112, 1st Paragraph

The Examiner has rejected claims 1-5, 7-10, 12-28 and 35-57 under 35 USC 112 for lack of enablement. It would appear that the Examiner's position can be summarized as there allegedly being no enabling support for the following:

1. Packaging systems other than Kunjin-based systems.
2. Non-structural protein mutations other than the particular mutations recited by former Claim 15.
3. Immunotherapeutic compositions or vaccines.

Given that Claim 25 has been amended to recite an immunogenic composition and former Claim 26 is deleted without prejudice in the interests of progressing allowance, we trust that point 3 above is rendered moot.

Furthermore, given that the limitations of former Claim 15 are now present in Claim 14, again made without prejudice in the interests of progressing allowance, we trust that point 2 above is also rendered moot.

We will therefore focus on the Examiner's assertion that there is allegedly no enabling support for packaging systems other than Kunjin-based systems. We respectfully disagree.

In this regard we point the Examiner to data in the specification at page 29 line 30 to page 31 line 21 which shows packaging of Dengue and West Nile (NY99) replicons by Kunjin structural proteins. The fact that a replicon of a distantly-related flavivirus, Dengue, is packaged by Kunjin virus packaging proteins (as shown in the data) makes it highly likely that replicons of other flaviviruses will be packaged as well. This is further supported by Kunjin packaging of a West Nile Virus replicon. The packaging strategy claimed and described in the present application was predicted to have wider applications to other flaviviruses which generally are more closely related to Kunjin than is Dengue. West Nile (NY99) is an example of a more closely-related flavivirus.

Since filing, numerous publications on chimeric flaviviruses have confirmed the predictions made in the present application. An example of a recent review of this field is provided in Hall & Khromykh, 2007, "Drug evaluation: ChimeriVax-West Nile vaccine, Current Opinion in Molecular Therapeutics", 9, 498-504 (cited in the accompanying IDS) which reviews and summarizes recent progress on chimeric flavivirus vaccines where structural proteins of one flavivirus are replaced by those from other flaviviruses. For example, flaviviruses from the same virus subgroup, such as replicons derived from any strain of West Nile virus, Japanese encephalitis virus and Murray valley encephalitis virus, will be packaged very efficiently. Many researchers use packaging systems for flavivirus replicons by providing structural proteins in trans from other expression vectors. The most recent examples include WNV and JEV replicon packaging systems where VEE replicons are used to express corresponding structural genes cassettes (C-prM-E), as for example published in Ishikawa et al., 2008, "Construction and evaluation of a chimeric pseudoinfectious virus vaccine to prevent Japanese encephalitis." Vaccine. 26 2772-81 (cited in the accompanying IDS) and Widman et al., 2008, "Construction and characterization of a second-generation pseudoinfectious West Nile virus vaccine propagated using a new cultivation system." Vaccine 26 2762-71 (cited in the accompanying IDS). We submit that work performed since the filing date has added to the actual data provided in the

present application in supporting broad claims to a packaging system where packaging proteins of one flavivirus can be used to package a replicon of a different flavivirus.

We therefore submit that there is little or no unpredictability about whether chimeric packaging systems can be used where packaging proteins of one flavivirus can be used to package a replicon of a different, even distantly-related flavivirus. Accordingly, we submit that the Examiner is not correct in asserting that "a large quantity of experimentation would be required" by a person of ordinary skill in the art in so far as creating a packaging system where packaging proteins of one flavivirus can be used to package a replicon of a different flavivirus. We therefore submit that Claims 1-14, 16-25, 27, 28 and 35-39 are indeed enabled.

Rejection under 35 USC § 102(b)

The Examiner has alleged that former Claims 1-28 and 35-37 are anticipated by WO 03/046189 (Khromykh).

The Examiner has alleged that Khromykh discloses a protein translation product encoding C, prM and E proteins in certain claims and also in Figures 10 and 11, Table 5, at page 12 lines 24-29, at page 14 lines 19-23 and at page 34 lines 19-25. Furthermore, the Examiner is of the view that the packaging system of Khromykh contained an RNA that encoded a heterologous protein and mutated non-structural proteins.

The Examiner has also alleged that the flaviviral packaging system disclosed by Khromykh comprises a tetracycline-repressible CMV promoter at page 18 lines 10-15, page 32 lines 30-31 and in Figure 9.

In response, we submit that in Fig. 10, separate protein translation products respectively encoding C and prM + E proteins were disclosed, resulting from transcription by separate 26S promoters. In Figure 11, a single protein translation product encoding C, prM and E proteins was disclosed, but in the context of a transiently-expressed RNA construct comprising a 26S promoter. Being in RNA form this construct did not, in fact could not, comprise a CMV promoter, tetracycline-repressible or otherwise.

With regard to the Examiner's comment that Khromykh comprises a tetracycline-repressible CMV promoter at page 18 lines 10-15, page 32 lines 30-31 and in Figure 9, we respectfully disagree.

The recitation at page 18 lines 10-15 relates to replicon expression using a CMV promoter operable in a a mammalian cell (for context, read lines 1-9 of page 18). Furthermore, there is no recitation that the CMV promoter is tetracycline-repressible or otherwise regulatable. This is not disclosure relating to CMV promoter-driven expression of structural proteins.

At page 32 lines 30-31 and Fig. 9 of Khromykh referred to by the Examiner, this disclosure relates to the SFV replicon construct pSFV3L713PlacZNeo. This is clearly stated at page 32 lines 30-31 and it is also clear from Fig. 9 that this is not a packaging construct encoding flavivirus C, prM and E proteins. Instead, it was used to stably transform BHK21 cells to work in conjunction with the packaging constructs of FIG. 10 and FIG. 11 to produce VLPs in the stably transformed BHK21 cells. Furthermore, this pSFV3L713PlacZNeo construct did not have a CMV promoter, let alone a tetracycline-repressible CMV promoter.

In summary, we submit that Khromykh did not describe or even suggest a packaging construct for regulatable expression of flavivirus structural proteins in an animal cell, said vector comprising a regulatable promoter operably linked to a nucleotide sequence encoding a flavivirus structural protein translation product that comprises C protein, prM protein and E protein. More particularly, Khromykh did not teach use of a tetracycline-repressible CMV promoter for stable expression of flaviviral structural proteins. Furthermore, Khromykh did not teach a packaging system, packaging cells or VLPs produced thereby, that utilized the claimed packaging construct. We therefore submit that Claims 1-14, 16-25, 27, 28 and 35-39 are novel over Khromykh.

Double Patenting

The Examiner has alleged that the claims of the present application are not patentable over several US filings that are either pending or granted, as follows:

1. US patent 6,893,866.
2. US patent application 11/098,233.
3. US patent application 11/816,350.

We understand that the Examiner requires a terminal disclaimer to be filed so that the eventual expiry date of the present application will conform to that of commonly-owned Replikun US patent 6,893,866.

We submit that the double patenting rejection is improper. It is our view that this presently claimed invention is patentably distinct over US patent 6,893,866. The presently claimed invention is predicated on the unexpected discovery that an inducible expression system for flavivirus packaging proteins, where the structural proteins are translated as a single translation product, produced up to a ~1500 fold improvement over previous packaging systems, such as described in US patent 6,893,866. This is unexpected and not derivable or otherwise obvious from the teaching of US patent 6,893,866. Moreover, at column 9 lines 43-53 of US patent 6,893,866, it is stated that "*To optimise expression of the flavivirus structural genes, the second vector might include such sequences as: sequences to promote expression of the genes of interest, including appropriate transcription initiation, termination, and enhancer sequences: as well as sequences that enhance translation efficiency, such as the Kozak consensus sequence. Preferably, the second vector contains separate regulatory elements associated with each of the different structural genes expressed by the vector. Most preferably, the flavivirus C gene and the prME genes are placed under the control of separate regulatory elements in the vector*" [emphasis added].

This disclosure teaches away from the present invention which shows unexpected benefits in placing the flavivirus C gene and the prME genes under the influence of a single promoter to thereby produce a single translation product comprising C, prM and E proteins.

We therefore submit that the presently claimed invention is non-obvious over commonly-owned US patent 6,893,866.

With regard to the provisional double patenting rejection based on US patent application 11/098,233 and US patent application 11/816,350, given the provisional nature of these rejections we respectfully request that they both be maintained in order to be considered and resolved at a later date.

CONCLUSION

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested. The Commissioner is hereby authorized to charge any additional fees required to Deposit Account No. 061910.

Respectfully submitted,

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